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Saul Ewing LLP (Philadelphia)
Attn: Patent Docket Clerk
Centre Square West
1500 Market Street, 38th Floor
Philadelphia, PA 19102-2186

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte PETER D. KATSIKIS, ALINA C. BOESTEANU, and MARTIN TURNER[1]

Appeal 2016-004225
Application 13/418,045
Technology Center 1600

Before DONALD E. ADAMS. FRANCISCO C. PRATS, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of inhibiting influenza virus replication, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

"PI3K represent a family of enzymes that phosphorylate D-myophosphatidylinositol (Ptdlns) or its derivatives" and are classified in 3 different classes "depending on their subunit structure, regulation, and

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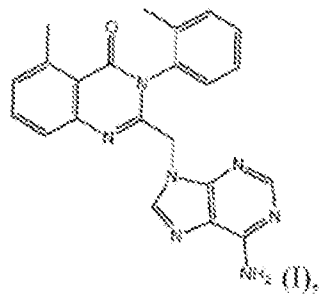
[1] Appellants identify the Real Party in Interest as Drexel University and The Babraham Institute. (Br. 3.)

substrate selectivity." (Spec. 2.) "PI3K belonging to class I are heterodimers composed of a catalytic subunit of approximately 110 kDa, and a tightly associated regulatory subunit that modulates the activity and cellular location of the enzyme." (*Id.* at 3.) The class I heterodimers exist in four isoforms, known as p110 alpha, beta, gamma, and delta. (*Id.*) The invention is directed to a method "for regulating Pl3K p110 delta kinase in a cell thereby providing a means for reducing or inhibiting retrovirus infection or replication in the cell." (*Id.* at 7.)

Claims 27, 30–33, 36–39, and 42–44 are on appeal.[2] Claim 27 is representative and reads as follows:

> 27. A method of inhibiting influenza virus replication in a mammalian cell, said method comprising contacting said cell with a therapeutically effective amount of a selective inhibitor of PI3K p110 delta,
>
> wherein said inhibitor inhibits influenza virus replication in said mammalian cell,
>
> wherein said inhibitor is a small molecule compound selected from the group consisting of INK1197, KAR4000, theophylline, CAL-101, CAL-263, Compounds (I)-(XXX), a mixture thereof, and a pharmaceutically acceptable salt thereof:

[2] Claims 28, 29, 34, 35, 40, and 41 are also pending, but stand withdrawn from consideration. (Br. 3.)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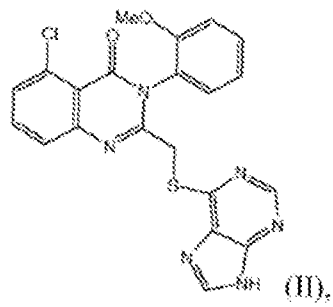
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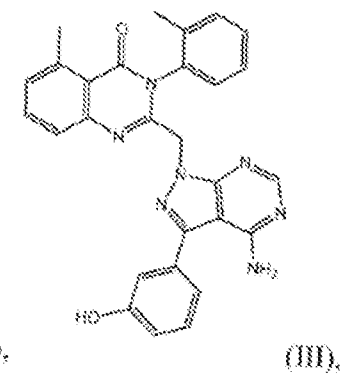
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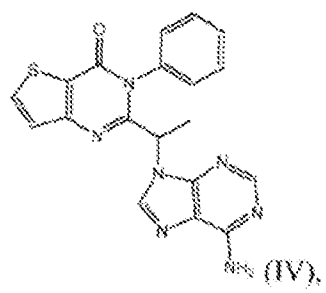
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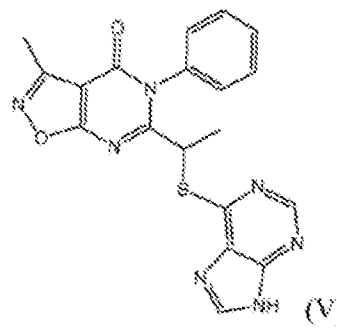
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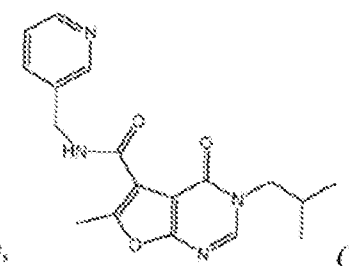
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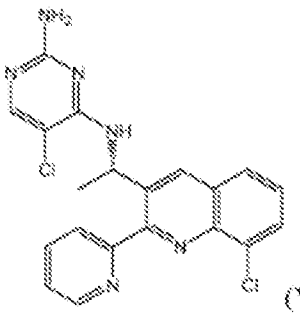

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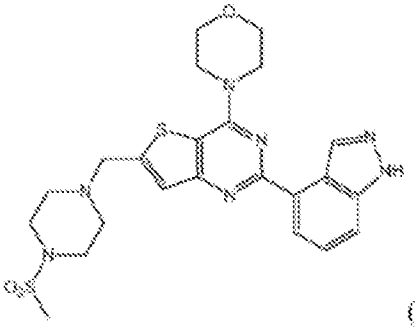

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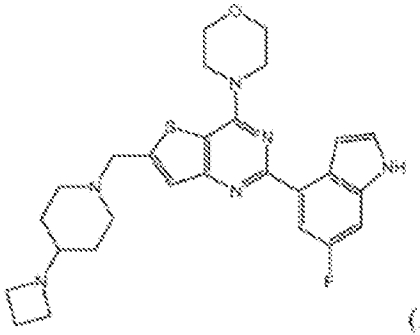

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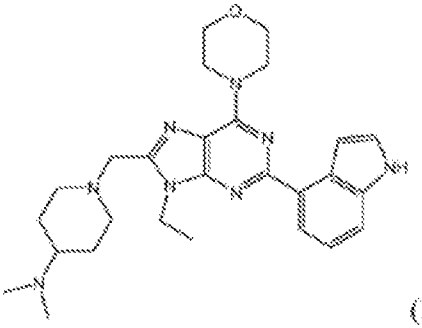

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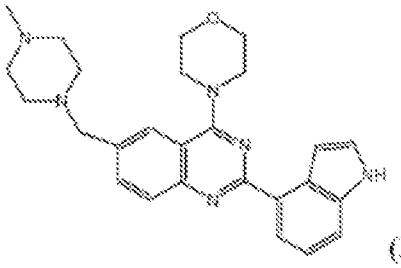

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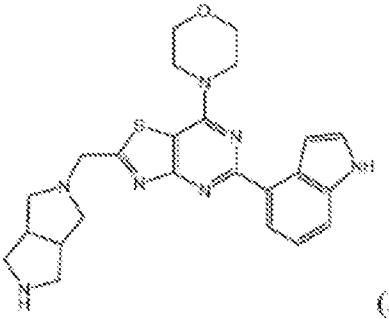

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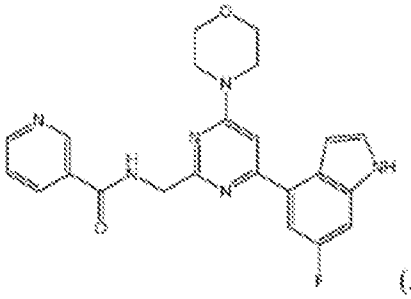

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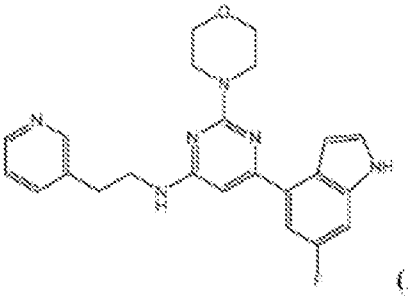

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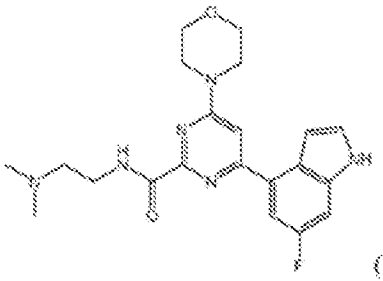

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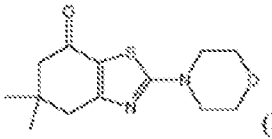

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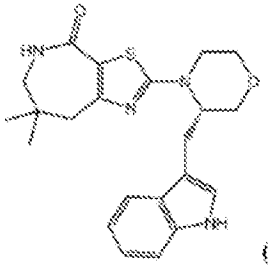

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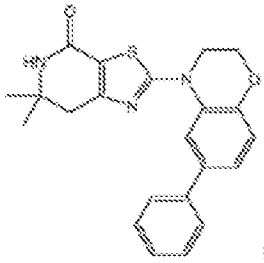

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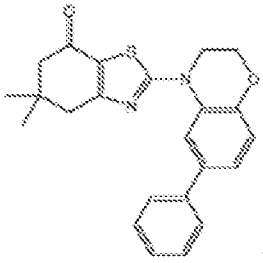

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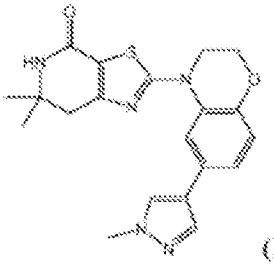

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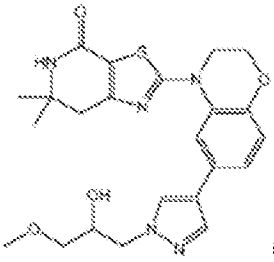

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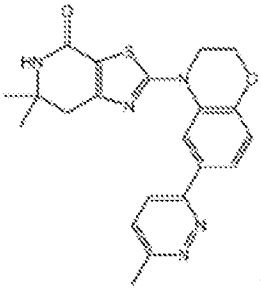

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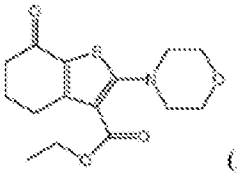

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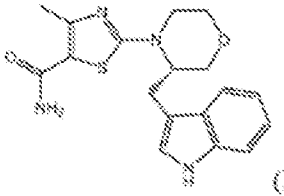

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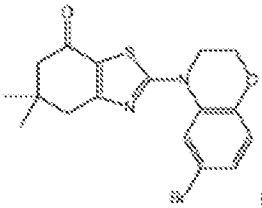

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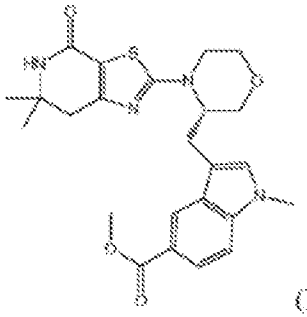

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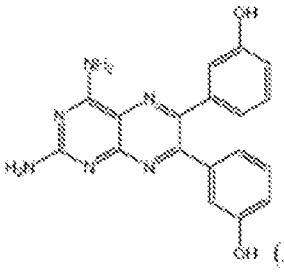

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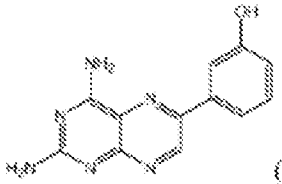

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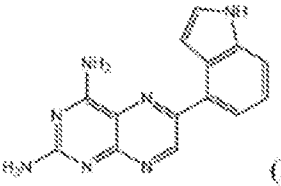

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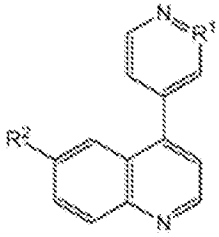

(XXX),

wherein in Compound (XXX):

R^1 is N or CH, and

R^2 is a substituent selected from the group consisting of 2,2-(5-thiazolidinyl-2,4-dione)-1-ethylenyl; phenyl; pyridin-2-yl; 1H-indaz-5-yl; 1H-pyrazolo[3,4-b]pyridin-5-yl; 2-amino-3-sulfonamido-pyridin-5-yl; 2-amino-3-[(N-2,4-difluorophenyl)sulfonamido]-pyridin-5-yl; 3-[(N-2,4-difluorophenyl)sulfonamide]-pyridin-5-yl; 3-(2,4-difluorobenzenosulfonylamino)-pyridin-5-yl; and 2-methoxy-3-(2,4-difluorobenzenosulfonylamino)-pyridin-5-yl.

(Br. 19–22.)

The following ground of rejection by the Examiner is before us on review:

Claims 27, 30–33, 36–39, and 42–44 under 35 U.S.C. § 103(a) as unpatentable over Diacovo,[3] Bengtsson,[4] Gruber,[5] and Carter.[6]

In response to a species election requirement, Appellants elected Compound I as the species of selective inhibitor of PI3K p110 delta. (Non-Final Action July 11, 2013; Response dated Oct. 11, 2013.) Accordingly, as to the appealed obviousness rejection, we limit our analysis to the patentability of the elected species and the extent to which the rejected claims read on it. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

DISCUSSION

Claim Construction

The Examiner finds that the preamble of the three independent claims—namely claims 27, 33, and 39 –reciting, respectively, "inhibiting influenza virus replication in mammalian cell," "inhibiting influenza virus pathogenesis in mammalian cell," and "treating influenza virus infection in a mammal," have not been given patentable weight "because the recitation occurs in the preamble" and preambles such as those recited are "not accorded any patentable weight where it merely recites the purpose of a

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[3] Diacovo et al. WO2006/089106 A2, published Aug. 24, 2006.
[4] Bengtsson et al., US 2008/0132502 A1, published June 5, 2008.
[5] Gruber et al., *Avian influenza (H5N1): implications for intensive care*, 32 Intensive Care Med. 823–29 (2006).
[6] Marissa J. Carter, *A rationale for using steroids in the treatment of severe cases of H5N1 avian influenza*, 56 J. Med. Microbio. 875–83 (2007).

process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." (Final Action 6.)

We do not agree with the Examiner's claim interpretation. Here, the claim preambles are intimately tied to the method. For example, in claim 27, the method requires contacting a mammalian cell with a selective inhibitor of P13K p110 delta in a therapeutically effective amount "wherein said inhibitor inhibits influenza virus replication" in the cell. In other words, the therapeutic amount is such that influenza virus replication inhibition in the mammalian cell that is contacted with the selective inhibitor must be achieved, which is also the purpose required by the claim preamble. Similarly, in claim 33, the method requires contacting a mammalian cell with a selective inhibitor of P13K p110 delta in a therapeutically effective amount "wherein said inhibitor inhibits influenza virus pathogenesis" in the cell. In other words, the therapeutic amount is such that influenza virus pathogenesis inhibition in the cell contacted must be achieved, which is also the purpose required by the claim preamble.

Claim 39 is slightly different, though the claim preamble is also intimately tied to the body of that claim. In claim 39, the method requires contacting a mammalian with a selective inhibitor of P13K p110 delta in a therapeutically effective amount "wherein said inhibitor interferes with [] P13K p110 delta activation and replication of said influenza virus" in the mammal, as well as "treats influenza virus." In other words, the therapeutic amount is such that not only is P13K p110 delta activation in the mammal interfered with, but interference with replication of the influenza virus in the mammal and treating the influenza virus infection must also be achieved.

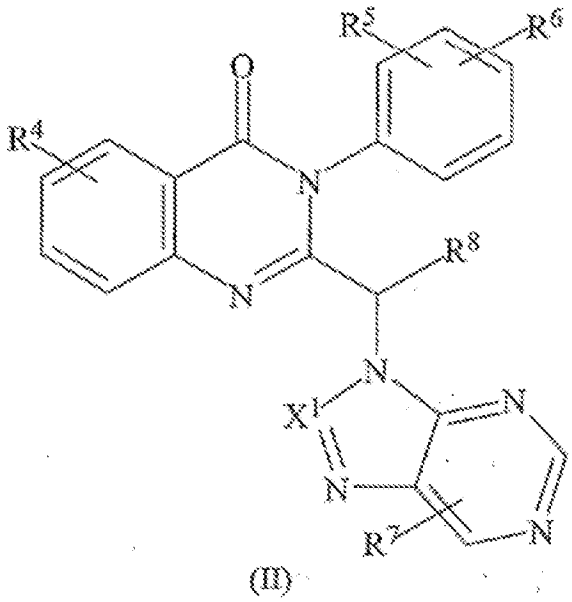
Thus, while the claim preambles are not a "separate limitation," *see, e.g.*, *Symantec Corp. v. Computer Assocs. Int'l, Inc.*, 522 F.3d 1279, 1288–89 (Fed. Cir. 2008), they serve to indicate that the "wherein" clauses recited in the body of the claim are tied into the therapeutically effective amounts so as to achieve the stated purpose in the wherein clauses, which are recited identically in the preamble. *See, e.g.*, *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) (finding that a "wherein" clause limited a process claim where the clause gave "meaning and purpose to the manipulative steps").

Nevertheless, we do not disagree with the Examiner that the preamble/wherein recitations "do not materially affect the steps of [the] claimed invention." (Ans. 6.) That is the single recited step of the method of treating influenza virus infection of claims 27 and 33 is "contacting said [mammalian] cell with a therapeutically effective amount of a selective inhibitor of P13K p110 delta." Claim 39 similarly recites a single step in the method of treating influenza virus infection, which is "administering a therapeutically effective amount of a selective inhibitor of phosphoinositide 3 kinase (PI3K) isoform p110 delta to said mammal." Appellants' Specification discloses that the "therapeutically effective amount" "may be in the range of from about 1 µg to about 10,000 mg" (Spec. 53) or that "suitable dose[s] of a compound of the present invention may be in the range of from about 0.01 mg to about 5,000 mg per day" and that the "dose may be administered in a single dosage or in multiple dosages, for example from 1 to 4 or more times per day" (Spec. 58).

II

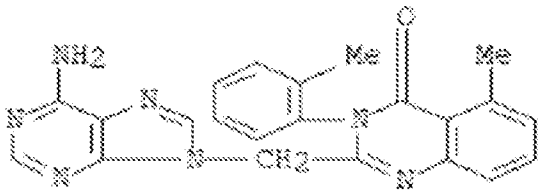
Obviousness

The Examiner finds that the claims 27, 33, and 39 are obvious from the teachings of Diacovo, Bengtsson, Gruber, and Carter. The Examiner finds that Diacovo teaches treating inflammation conditions in the respiratory system caused by pathogens, including virus, by inhibiting PI3K p110 delta and PI3K p110 gamma with compounds of general formula II



(II)

and, in particular, using the compound having the formula



, also known as IC87114, which is a compound within the scope of the claims. (Final Action 2–3; Spec. 30 ("Compound (I) (IC87114 or 2-[(6-amino-9H-purin-9-yl)methyl]-5-methyl-3-(o-tolyl)quinazolin-4(3H)-one)).") The Examiner notes that while

Diacovo does not expressly teach treating patients with influenza infection, it does disclose inflammatory conditions include adult respiratory distress syndrome ("ARDS"), and Bengtsson teaches treating a human with a respiratory tract condition caused by influenza virus infection through the administration of a small molecular compound that inhibits P13K-delta. (Final Action 3–4.) The Examiner further explains that Gruber teaches that ARDS is known to result from avian influenza, and Carter "teaches that imbalance of pro-inflammatory and anti-inflammatory cytokines is believed to be responsible for the development of ARDS and anti-inflammatory agents are known to be used for treating inflammatory condition caused by avian influenza." (*Id.* at 3) In short, the Examiner finds that

> [t]he prior art as a whole teach the compounds herein known as inhibitors of PI3K p110 delta and/or PI3K p110 gamma are useful for treatment of inflammatory conditions in respiratory tract, particularly those caused by viral infection, such as ARDS, an advanced conditions commonly caused by influenza infection. Therefore, it would have been obvious to use such a compound for treatment of ARDS caused by influenza infection.

(Ans. 5–6.) We agree with the Examiner's findings regarding the teachings of the prior art and the conclusion that these teachings render the claimed invention obvious.

Appellants argue that the Examiner has clearly erred in not considering the preamble/wherein clause. (Br. 8–9.) We are not persuaded that the Examiner did not consider that limitation. The Examiner specifically pointed to Example 13 of Diacovo, which discusses administration of particular amounts of IC87114 to mice (10 μM in Example 13) and which demonstrates that IC87114 reduces "neutrophil attachment to

and rolling on inflamed venular endothelium." (Diacovo ¶¶ 254–256.) The Examiner noted that Appellants have not established the preamble/wherein limitations "materially affect the steps of [the] claimed invention," (Final Action 6; Ans. 6), *i.e.*, contacting the cells with a therapeutically effective amount, or administering a therapeutically effective amount.

As we noted above, Appellants' Specification indicates a large variation of dosage amounts are effective to achieve the claimed therapeutic effect, including as low as 1 µg. (Spec. 53.) Appellants do not contend that administration of equivalent amounts of the dosages described in Diacovo that reduce "neutrophil attachment to and rolling on inflamed venular endothelium" (Diacovo ¶¶ 254–256)—and which we find would reasonably be expected to treat inflammation—to achieve the same result in humans, which dosing in humans the Examiner finds is suggested by Bengtsson (Bengtsson ¶ 346), would not achieve the claimed result, just that none of the references discuss achieving that result. However, just as "a patent on a composition or machine cannot be predicated on a new use of that machine or composition," *In re Hack*, 245 F.2d 246, 248 (CCPA 1957), "[i]t is a general rule that merely discovering and claiming a new benefit of an *old* process cannot render the process again patentable," *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990).

It is undisputed that IC87114 directly blocks the function of p110 delta, and that was known in the prior art. (Diacovo ¶ 255.) Appellants' Specification teaches that "[t]he invention comprises compositions and methods for modulating PI3K p110 delta in a cell thereby inhibiting the PI3K p110 delta response in the cell." (Spec. 32.) Appellants' invention appears to be the discovery that in addition to the functions disclosed in

Diacovo, i.e., that selective inhibitors of P13K p110 delta, such as IC87114, may be involved in inhibiting leukocyte accumulation by inhibiting upstream targets in pathways that selectively activate P13K p110 delta in endothelial cells (Br. 10; Diacovo ¶ 28), inhibiting leukocyte tethering to endothelial cells (Diacovo ¶ 35), inhibiting leukocyte transmigration by inhibiting P13K delta in endothelial cells (Diacovo ¶ 36), or "inhibit[ing] or reduc[ing] AKT-activity of endothelial cells, *e.g.*, as measured by AKT-phosphorylation . . . [or] PDK1 enzyme activity of endothelial cells" (Diacovo ¶ 37), this compound can also inhibit retroviral infection in the cell (Spec. 33, 45). That a person of ordinary skill in the art would not have known of the effect also does not preclude a finding of obviousness. *PAR Pharm. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197 (Fed. Cir. 2014). That is because "we are not limited to the same motivation that may have motivated the inventors." *Id.* Thus, we also do not find Appellants' argument that "[w]ithout the teachings of the present invention, at the time of the invention one skilled in the art would not have been able to tell or foresee ***which*** p110 catalytic subunit in a cell should be inhibited in order to interfere with influenza virus infection or replication." (Br. 14.)

As noted above, the claimed process includes one step: administering one of the recited compounds, which include IC87114 disclosed in Diacovo. We agree with the Examiner that the prior art relied on provides motivation to treat patients having respiratory tract inflammation, such as ARDS, caused by avian flu, with a selective inhibitor of P13K p110 delta, such as IC87114. That "ARDS is a possible, but not certain, complication" of individuals infected with avian influenza (Br. 11) is immaterial to whether the prior art provides the requisite motivation to treat a patient population

that in fact has ARDS. One of ordinary skill in the art would have been motivated to combine the teachings of the cited reference to use IC87114 for treating patients with ARDS, or other respiratory inflammatory conditions caused by influenza.

Furthermore, that Diacovo teaches selective inhibitors of P13K p110 gamma in addition to selective inhibitors of P13K p110 delta (Br. 10) does not derogate from the fact that it teaches a selective inhibitor of P13K p110 delta that would result in selective inhibition of P13K p110 delta. Indeed, Diacovo teaches the same selective inhibitor of P13K p110 delta disclosed for use that Appellants disclosed and claim, i.e., IC87114. (*See, e.g.*, Spec. 27.)

We also do not find the argument that Bengtsson does not "teach the inhibition of PI3K delta" (Br. 11, 13, 14) persuasive of nonobviousness. "Non-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). And, "[o]bviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988).

That Diacovo also teaches selective inhibition of P13K p110 gamma in addition to P13K p110 delta, does not teach away from the claimed invention (Br. 13). "The transition 'comprising' in a method claim indicates that the claim is open-ended and allows for additional steps." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003).

Appellants' method claims use the open ended transition phrase "comprising" and thus do not preclude the additional administration of a selective inhibitor of P13K p110 gamma.

As discussed, one of ordinary skill in the art need not have a reasonable expectation of success of inhibiting viral replication in order to make the Examiner's combination. *PAR Pharm.*, 773 F.3d at 1197. For the reasons discussed above, Appellants' arguments are unpersuasive to establish that there would not have been a reasonable expectation of success of treating inflammation due to avian flu virus with IC87114.

For the foregoing reasons, we are not persuaded that the Examiner erred in maintaining the obviousness rejection of claims 27, 33, and 39.

Claims 30, 32, 36–38, and 42–44 have not been argued separately (Br. 15–17 (noting that the dependent claims are not obvious "[f]or the same reasons set forth above regarding" the independent claims 27, 33, and 39)), and therefore fall with claims 27, 33, and 39. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of claims 27, 30–33, 36–39, and 42–44 under 35 U.S.C. § 103(a) as unpatentable over Diacovo, Bengtsson, Gruber, and Carter.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED